REMARKS

Applicants have discovered that immunization with rough complete core LPS (particularly with a cocktail containing rough complete core LPS from more than one strain) provides protection against endotoxemia. Protection is afforded not only against strains bearing an LPS present in the vaccine, but also from other strains. In so doing, Applicants have challenged the conventional wisdom favoring use of smooth LPS that includes O-linked side chains, which were thought to be better immunogens. Applicants' discovery also runs contrary to the idea of using various incomplete core LPS's. Figs. 1 and 2 show the various types of gram-negative LPS structures.

Applicants' findings are important given: a) the large number of clinically relevant bacteria; b) the impracticality of immunizing with all possible O-linked side chain-containing LPS; and c) the absence of documented cross-reactivity between antibodies to specific O-linked side chains.

No prior art rejections remain in this case.

I. 35 U.S.C. 112 ¶1

All pending claims are rejected under 35 U.S.C. 112 ¶1 as not enabled. This is a scope-of-enablement rejection.

As detailed below, at this advanced stage of prosecution the only remaining issue appears to be proof that vaccines according to the invention in fact protect animals. The original rationale for the rejection is presented in paper 13 at page 4. Subsequent actions maintain the rejection based on that original rationale. The rationale is,

> ...the specification while being enabling for production [of] antibodies by immunizing with compositions comprising rough complete-core LPS, does not reasonably provide enablement for treatment of animals by reducing the adverse effects of endotoxin. [Emphasis is added.]

After listing the factors from In re Wands the office action goes on to apply three of those factors:

The nature of the invention – methods of reducing the adverse effects of endotoxin in warm blooded animals, i.e., *in vivo* treatment, comprising administration of a composition comprising rough, complete-core LPS.

The state of the prior art – high concerning immunization with gram negative bacteria.

The amount of direction or guidance present – While the instant specification discusses the adverse effects which are imparted by endotoxin and the structure of smooth and rough core LPS, the specification is silent concerning examples of treatment of animals to reduce the adverse effects of endotoxin. The specification teaches antibody production and *in vitro* binding assays. The specification [includes?] no examples concerning the dosage, timing of administration, etc. which are the necessary parameters for determining the proper steps to fulfill the methods claimed.

After reviewing the above record, Applicants first ask for guidance on the Examiner's distinction between "immunization" and "treatment". The claim language is "A method of reducing the adverse effects...which comprises administering...." In effect, the claims are directed to administration to develop a protective immune response – i.e. immunization. Applicants request clarification as to the distinction between "immunization" and "treatment by administration". Guidance is specifically requested as to whether the rejection would be obviated by amending the claims to specify, "A method of immunization with a composition..." It is not understood why admittedly enabled techniques for immunization are not adequate to support the claims in this case.

In the absence of guidance on that point, Applicants have sought to respond to the rejection by focusing on the breadth of the definition of the immunogen administered according to the claims. Applicants have twice limited the claims (the claims now specify using LPS from rough complete core strains of *E. coli, Pseudomonas,* and *Bacteroides*), yet the examiner maintains the rejection based essentially on the same analysis – the absence of enablement of treatment of animals.

> The specification...utilizes only either a liposomal composition consisting only of purified *E. coli* specific strain K12 LPS or a cocktail of purified LPS from only *E. coli* K-12, *E. coli* R1, *P. aeruginosa* PAC608 and *B. fragilis* LPS.

The Examiner characterizes what is missing as follows:

> There is insufficient support for the instant claims, i.e., treatment of animals utilizing a composition comprising rough complete-core LPS antigens from ≥ 2 bacteria of strains of *E. coli, Pseudomonas,* and *Bacteroides*.

The claims are already limited to the use of a cocktail of rough complete-core LPS antigens from ≥ 2 bacteria of strains of *E. coli, Pseudomonas,* and *Bacteroides*. The accompanying declaration of one of the inventors, Dr. Bennett-Guerrero, establishes that a vaccine comprising a cocktail of LPS complexes from different bacterial strains protects animals from a challenge with LPS from a different bacterial strain. This cross-reactivity is evidence that the invention is not limited to any specific strain or isolate of bacteria.

Nor is the use of liposomes a critical feature. In the experiments that Dr. Bennett-Guerrero reports, the LPS's were not packaged in a liposome. The Examiner has offered absolutely no reason to think that the invention should be limited to use of liposomal formulations. Clearly the teachings in the specification are not limited in that way.[2]

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[2] At page 10:21-26 the specification provides the following guidance about how to practice the invention using vaccines that do not include liposomes,

> Alternatively the LPS antigen can be in the form of purified LPS or complexed to an acceptable carrier. Appelmelk et al., *J. Immunol. Meth.*, 82:199 (1985). The antigen may be chemically detoxified. The bacterium may be genetically engineered for various reasons, e.g., to reduce toxicity. The composition may also include an adjuvant, e.g., alum.

Similarly, at page 14:8-21 the specification says,

> If whole bacteria are to be included in the vaccine the bacterium will be killed by a technique well known to those in the art, such as heat killing or formaldehyde killing. In this case, the entire LPS of rough mutant bacterium will be included as part of the killed bacterium. It is desirable to avoid bacterial killing methods which can alter the core.
>
> Alternatively, complete core LPS can be isolated from the desired bacteria according to standard techniques as outlined by Hancock et al., BACTERIAL CELL SURFACE TECHNIQUES, pp. 91 (John Wiley & Sons 1988). As noted, it is preferable to include all of the core LPS, without the O-polysaccharide outer LPS structures, i.e. use R-mutant bacteria expressing full LPS core.

From that disclosure in the application as filed, the art would understand that the LPS can be complexed to a carrier and that liposomes are not essential to the invention.

Moreover, Applicants have discovered that such a cocktail can provide protection against a challenge by LPS from strains other than those used to make the vaccine. Dr. Bennett-Guerrero's Declaration also establishes that the invention is not limited to any specific strain.

II. 35 U.S.C. §112 ¶2

The Office Action rejects claims 97 and 98 as incomplete for omitting what the Examiner characterizes as "essential steps". Reference is made to the previous office action (paper 16) indicating that the applicants must limit the claims further to actual quantitation steps such as desktop scanners, Adobe Photoshop®, and a computer software program (as opposed to quantitation by staining). Applicants apologize for failing to respond to this rejection in their last response.

The Examiner's conclusion that the claims should be limited to the use of proprietary software and commercially available apparatus that has nothing to do with the invention legally and factually unsupported. The statute (35 U.S.C. §112 ¶2) does not authorize the Examiner to arbitrarily limit claims to minute details in the specification. All the statute requires is claims with reasonably definite metes and bounds. Those skilled in the art must know what the claim covers and what it does not. For example, in *Carl Zeiss Stiftung* v. *Renishaw PLC*, 945 F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991) the Federal Circuit made clear that claims need not teach the art how to practice the invention. That is the function of the specification, not the claims. In that case, the Federal Circuit reviewed a finding that a claim was invalid under 35 U.S.C. 112 ¶2 because the claim "omits any electrical circuitry or other signalling means...[and] the arbitrary presentation of *part* of an invention does not constitute a claim of a valid invention...." *Stifung v. Renishaw PLC,* 945 F.2d at 1181. The Federal Circuit was adamant that this type of rejection is improper.

> ...[I]t is entirely consistent with the claim definiteness requirement of the second paragraph of section 112, to present "subcombination" claims, drawn to only one aspect or combination of elements of an invention that has utility separate and apart from other aspects of the invention.... "it is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter" and it is "entirely appropriate, and consistent with § 112, to present claims to only [one] aspect. *Bendix Corp. v. United States*, 600 F.2d 1364, 1369, 220 Ct.Cl. 507, 514, 204 USPQ 617, 621

> (1979). Thus, the holding of invalidity that rests on a conclusion of lack of claim definiteness is legally incorrect. [Footnote omitted] Furthermore, the district court erred in looking only to the descriptive part of the specification to determine what McMurtry invented. It is to the claims which particularly point out what the inventor regards as his invention that one must look, and each claim must be considered separately. *Stifung v. Renishaw PLC,* 945 F.2d at 1181.

The Examiner makes no attempt whatsoever to explain why the scope of the claim is in any way unclear or why the Applicants must narrow an otherwise valid claim to specify a particular proprietary software and commercially available apparatus. Such limitations are arbitrary and have no foundation in the statute. Applicants respectfully request the Examiner to apply the above law to this case and to withdraw the rejection under §112 ¶2.